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TITLE: A BIFUNCTIONAL DTPA-TYPE LIGAND.
EIN BIFUNKTIONELLER LIGAND DES DTPA TYPS.
LIGAND DU TYPE DTPA BIFONCTIONNEL.

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REF. NON-PATENT-LIT.: JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1 vol. 9, 1992 pages 1173 - 1178 M.W. BRECHBIEL ET AL. 'SYNTHESIS OF C-FUNCTIONALIZED TRANS-CYCLOHEXYLDIETHYLEN ETRIAMINEPENTA-ACETIC ACIDS FOR LABELLING OF MONOCLONAL ANTIBODIES WITH THE BISMUTH-212 alpha-PARTICLE EMITTER' JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS vol. 17, September 1991 pages 1169 - 1170 M. W. BRECHBIEL ET AL. 'AN EFFECTIVE CHELATING AGENT FOR LABELLING OF MONOCLONAL ANTIBODY WITH 212BI FOR alpha-PARTICLE MEDIATED RADIOIMMUNOTHERAPY' ACTA RADIOLOGICA vol. 374, no. SUP., 1990 pages 135 - 140 S.C. SRIVASTAVA ET AL. 'DEVELOPMENT OF A NEW RADIOLABEL (203PB) AND A NEW CHELATING AGENTS FOR LABELLING MONOCLONAL ANTIBODIES FOR IMAGING' THE JOURNAL OF NUCLEAR MEDICINE vol. 29, 1988 pages 1324 - 1325 R.C. MEASE ET AL. 'THE SYNTHESIS OF SEMI-RIGID POLYAMINOCARBOXYLATES AS NEW BIFUNCTIONAL CHELATING AGENTS' CANCER RESEARCH vol. 49, no. 10, 1989 pages

- 2644 R.W. KOZAK ET AL. 'NATURE OF THE BIFUNCTIONAL CHELATING AGENT USED FOR RADIOIMMUNOTHERAPY WITH YTTRIUM-90 MONOCLONAL ANTIBODIES: CRITICAL FACTORS IN DETERMINING IN VIVO SURVIVAL AND ORGAN TOXICITY' Inorganic Chemistry, Vol. 25, No. 16, issued 1986, BRECHBIEL et al., "Synthesis of 1-(p-Isothiocyanato-benzyl) Derivatives of DTPA and EDTA. Antibody Labeling and Tumor-Imaging Studies", pages 2772-2781, see 2nd column on page 2772

DETDEN. . . be chelated. (Krejcarek et al., Biochem. Biophys. Res. Commun. 77:581, (1987); Brechbiel et al., Inorg. Chem. 25:5783 (1986)). Imaging of **tumor** target sites in vivo with metal chelate conjugated monoclonal antibodies prepared according to these methods has been reported. (Khaw et al., Science 209:295, (1980); Sheinberg et al., Science 215:151, (1982)). Diagnosis of human **cancer** in vivo using metal chelate conjugated monoclonal antibody has also been reported. (Rainsbury et al., Lancet 2:694 (1983)). The use. . . However, attempts to employ the **tumor** localizing properties of metal chelate conjugated monoclonal antibodies for therapeutic purposes have not found common usage. This is, in part,. . . strong metal chelates to firmly link radiometals to monoclonal antibodies and of rigorous purification of the conjugates to effect maximal **tumor** localization and minimize delivery to non-target tissues is discussed in

Brechbiel et al., Inorg. Chem. 25:2772-81 (1986)). Undesirable localization of. . .

Disubstituted bifunctional DTPA derivatives have proven useful for the labeling of proteins with radioactive metals (Kozak, et al., **Cancer** Research 49:2639-44 (1989)). The introduction of a second substituent on the carbon backbone of DTPA was seen to retard the. .

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The usefulness of radionuclide materials in **cancer** therapy is disclosed in the article, Kozak et al., "Radionuclide-conjugated monoclonal antibodies: A Synthesis of Immunology, in Organic Chemistry and. . .

In addition, the invention includes a **ligand-hapten conjugate** comprising: <image> wherein

n is an integer from 1 to 5;

X' is NH-Q, NHCS-Q or -NHCOCH.sub2.-Q where. . .

Another embodiment of the invention includes the **ligand-hapten conjugate** wherein n is an integer from 1 to 5, X' is -NH-L-Q, -NHCS-L-Q, or -NHCOCH.sub2.-L-Q, where Q is a hapten. .

.

A further embodiment includes the situation where L of the **ligand-hapten conjugate** is selected from the group consisting of an organic radical, or a substituted aliphatic hydrocarbon chain. The chain may be. . .

A further embodiment includes the metal chelates of the **ligand-hapten conjugate** wherein n is an integer from 1 to 5, X' is equal to -NH-Q, -NHCS-Q or -NHCOCH.sub2.-Q, where Q is. . .

An additional embodiment includes the metal chelates of the **ligand-hapten conjugate** wherein n is an integer from 1 to 5, X' is equal to -NH-L-Q, -NHCS-L-Q or -NHCOCH.sub2.-L-Q, where Q is. . .

The present invention also includes the method of using the metal chelates of the **ligand-hapten conjugate** wherein said **conjugate** is administered to a patient as a

therapeutic agent or diagnostic agent.
Furthermore, the present invention includes the method of using the metal chelates of the **ligand-hapten conjugate** possessing a linking group wherein the chelate as a therapeutic or diagnostic agent.
Monoclonal . . . function and specificity, and such antibodies can be
and have been developed for a wide variety of target antigens, including
tumor cells. More recently, chimeric monoclonal antibodies and fragments have been prepared by recombinant techniques (Morrison, S.L., Hospital Practice (Office Edition). . .
A . . . stable in vivo. Such complexes of other substituted DTPA ligands are not stable in vivo, thus precluding their use in **cancer** therapy when linked to antibodies.
An . . . invention is that they form stable complexes in vivo with a wide variety of other radiometals which are used in **cancer** detection and therapy. Such metal ions include trivalent indium, yttrium, or scandium and divalent lead and copper. Indium-111 is often used for **tumor** imaging. Thus, a patient could be imaged with the In-111 antibody conjugate of the ligand of this invention and thereafter. . . bismuth-212 complex of the same antibody chelate conjugate, thus facilitating calculation of the dose of radioactivity transported to the patients **tumor** and so increasing likelihood of the effective application of the therapy. With dosimetry information,
multiple dosing therapies can be designed.. . .
A further embodiment of the invention is a **ligand-hapten conjugate** as is drawn in Formula II (shown above) in which the T in the cyclohexane ring denotes the trans isomer. . .
The . . . or metal content to be utilized for any application will also depend upon the particulars of that application. In treating **tumors**, for example, the dose will depend, inter alia, upon **tumor** burden, accessibility and the like. Somewhat similarly, the use of metal chelate conjugated antibodies for diagnostic purposes will depend, inter. . .

CLMEN 3. A **ligand-hapten conjugate** comprising:
<image> wherein
n is an integer from 1 to 5;
X' is NH-Q; NHCS-Q or -NHCOCH.sub2.-Q where. . .
4. A **ligand-hapten conjugate** of formula II shown in claim 3, wherein X' is -NH-L-Q, -NHCS-L-Q or -NHCOCH.sub2.-L-Q,
L being a covalent linking group,. . .

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